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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/529,221	06/30/2006	Bruno Robert	1843.0200001/EKS/AJK	2116

26111 7590 08/31/2009

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EXAMINER
DIBRINO, MARIANNE NMN

ART UNIT	PAPER NUMBER
1644	

MAIL DATE	DELIVERY MODE
08/31/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/529,221	ROBERT ET AL.	
	Examiner	Art Unit	
	MARIANNE DIBRINO	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *9/8/05, 6/2/09, 2/23/09*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-48* is/are pending in the application.

4a) Of the above claim(s) *5-7,9,12-39 and 41-48* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,8,10,11 and 40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 March 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :8/15/06,4/9/07,11/6/07,3/12/08.

DETAILED ACTION

1. Applicant's amendment filed 9/8/05, Applicant's response filed 6/2/09 and Applicant's amendment and response filed 2/23/09 are acknowledged and have been entered.

2. The disclosure is objected to because of the following informalities:

There are spelling errors at [0160] and [0161] as a square symbol is used in a variety of chemical names rather than a letter or number. Applicant is required to explain the errors and not add any new matter.

Appropriate correction is required.

3. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which Applicant may become aware in the specification.

4. Applicant's election with traverse of Group I and without traverse of the species of CD1d complex comprising the antigen α–GalCer fused to an scFv antibody fragment with specificity for Her2/neu, and wherein the said complex does not further comprise a costimulatory molecule, in Applicant's amendment and response filed 2/23/09 and Applicant's response filed 6/2/09.

The basis for Applicant's traversal, briefly stated, is that a corresponding special technical feature that is common to Groups I and II is the use of compounds comprising CD1d/β2m complexes linked to an antibody or fragment thereof specific for cell surface markers, and that this feature is present in all of the pending claims and therefore links the claims as a single general inventive concept under PCT Rule 13.1. Applicant further argues that the primary reference does not teach CD1d/β2m/antibody complexes that specifically target cells expressing cell surface markers, but rather discusses CD1d fusion polypeptides used to screen and identify CD1-restricted T cells and novel CD1 antigens. Applicant argues that the secondary reference also does not teach the use of compounds comprising CD1d/β2m complexes linked to an antibody or fragment thereof specific for cell surface markers, that the genes encoding CD1d are located on a different locus than those encoding MHC molecules although they share structural similarities, and does not teach the use of CD1d associated with glycolipid antigens or targeting an innate immune response to a cell surface marker.

Applicant's arguments have been fully considered, but are not persuasive.

First, although the inventions of Groups I and II require the technical feature of a CD1d complex linked to an antibody or fragment thereof, this technical feature is not a special technical feature as it does not make a contribution over the prior art, as enunciated at item #2 on pages 2-3 of the requirement for restriction/election mailed on 1/21/09.

Second, with regard to the remainder of Applicant's arguments, Applicant is arguing the references separately. In response to Applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Third, Applicant's argument concerning the genes encoding CD1d *versus* those encoding MHC molecules is off-point, as the art taught, and the skilled artisan was aware as well, at the time the invention was made that CD1d and MHC class I molecules share not only structural similarities, but also functional similarities: both bind and present antigens to T cells, stimulating said T cells.

The requirement is still deemed proper and is therefore made FINAL.

Accordingly, claims 5-7, 9, 12-39 and 41-45 (non-elected species of Group I) and claims 46-48 (non-elected Group II) are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to non-elected inventions.

Claims 1-4, 8, 10, 11 and 40 are currently being examined.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-4, 8, 10, 11 and 40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Claim 1 is indefinite in the recitation of "an antibody or fragment thereof specific for a cell surface marker because it is not clear what is meant, *i.e.,* if the fragment or the antibody or both are antigen-binding.

Claim 8 is indefinite in the recitation of "wherein said antibody or fragment thereof is a scFv fragment" because it is not clear what is meant, *i.e.,* how an intact antibody can be a fragment of an antibody.

Claim 40 is indefinite in the recitation of "said CD1d complexes" because it is not clear what is meant with regard to just one CD1 complex, *i.e.,* base claims 1 and 2 recite "one or more CD1d molecules". Claim 40 lacks a reference to one CD1d molecule.

7. For the purpose of prior art rejections, the filing date of the instant claims 1-4, 8, 10, 11 and 40 is deemed to be the filing date of PCT/US03/30238*, i.e.,* 9/26/03, as the foreign priority application EPO 02405838.0 does not support the claimed limitations of the instant application. The said parent application does not provide support for a compound comprising greater than one CD1d complex, nor for an antibody with specificity for Her2/neu or the other cell surface markers recited in instant claim 11.

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 1-4, 10, 11 and 40 are rejected under 35 U.S.C. 103(a) as being obvious over Donda *et al* (Cancer Immunity 8/03, 3: 11) in view of US 2002/0071842 A1 (of record) and Fujii *et al* (Nature Immunology, 9/02, 3(9): 867-875).

Donda *et al* teach *in vivo* targeting of an anti-tumor antibody coupled to an antigenic MHC class I complex to induce specific growth inhibition and regression of established syngeneic tumor grafts. Donda *et al* teach that their strategy combined the advantage of the well-documented tumor targeting properties of anti-tumor antigen (*i.e.,* anti-TAA) mAbs with the known efficient and specific cytotoxic activity of CD8 T lymphocytes directed against highly antigenic MHC/peptide complexes, *i.e.,* using a Fab' fragment from a high affinity anti-TAA mAb coupled to a MHC class I containing a selected antigenic peptide in order to target the active MHC/peptide complex on tumor cells and induce their lysis by specific CTLs. Donda *et al* further teach using an anti-ErbB-2 antibody coupled to an MHC/peptide complex (*e.g.,* ErbB-2 is also known as Her2/neu) (see entire reference).

Donda *et al* do not teach wherein the compound used for targeting and tumor cell destruction comprises a CD1d complex rather than an MHC complex, nor wherein the antigen bound to the CD1d molecule is α-GalCer.

US 2002/0071842 A1 discloses a CD1d-IgG fusion protein comprising a tumor antigen, or alternately comprising α-GalCer as the antigen, that binds to CD1d, and administration of a composition comprising such in order to enhance or induce protective immunity to a condition associated with the presence of the tumor antigen (*i.e.,* a cancer). US 2002/0071842 A1 discloses that CD1 molecules are evolutionarily conserved β2m-associated proteins, with a similar domain organization to class I MHC antigen presenting molecules, although CD1 molecules have a deeper and more hydrophobic antigen binding groove that do class I MHC molecules. US 2002/0071842 A1 discloses that correspondingly, while class I MHC molecules present peptide antigens, CD1 molecules can present lipids, phospholipids and glycolipids, and both human and murine CD1d molecules have been shown to present α-GalCer, a synthetic acylphytosphingolipid originally isolated from a marine sponge, and that this latter antigen is recognized by CD1d-restricted NKT cells (especially Abstract, [0011], [0012], [0030], [0031], [032]-[0035], [0039], [0055], [0080]-[0083], [0095], [0101], [0124], [0127]-[0129], [0138], [0153], [0156], [0158], and claims).

Fujii *et al* teach that NKT lymphocytes are implicated in control of resistance to tumors and that a subset of NKT cells that have an invariant TCR are restricted to CD1d. Fujii *et al* further teach that α-GalCer binds to and is presented by CD1d to NKT cells, thus having anti-tumor activity. Fujii *et al* teach that it is preferable to administer α-GalCer – pulsed dendritic cells (that express CD1d) *versus* administering free α-GalCer because the response was stronger, more prolonged and was associated with increased protection against the development of metastases with melanoma (especially abstract, introduction and discussion sections).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have constructed an antibody or antigen-binding antibody fragment-targeted-complex with specificity for the cell surface marker Her2/neu (ErbB-2) similar to that taught by Donda *et al*, but rather making a CD1d/β2m/α-GalCer complex by engineering a fusion protein of CD1d with the antibody or antigen-binding fragment thereof with specificity for a cell surface marker such as the tumor antigen Her2/neu (ErbB-2) and loading α-GalCer into the antigen binding site of CD1d/β2m.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to produce a compound that could target tumor cells expressing Her2/neu with the said compound in order to protect against targeted tumors by activation of NKT cells, particularly in light of the teaching of Fujii *et al* that α-GalCer binds to and is presented by CD1d to NKT cells that are useful in controlling resistance to tumors, and in light of the disclosure of US 2002/0071842 A1 that an CD1d-IgG fusion protein comprising α-GalCer is useful to enhance or induce protective immunity to cancer.

10. Claim 8 is rejected under 35 U.S.C. 103(a) as being obvious over Donda *et al* (Cancer Immunity 8/03, 3: 11) in view of US 2002/0071842 A1 (of record) and Fujii *et al* (Nature Immunology, 9/02, 3(9): 867-875) as applied to claims 1-4, 10, 11 and 40 above, and further in view of Pavlinkova *et al* (Cancer immunology and immunotherapy, 2000, 49(4-5): 267-275).

The combination of Donda *et al* in view of US 2002/0071842 A1 and Fujii *et al* has been discussed supra.

The said combined references do not teach that the targeting antibody is an scFv fragment of the antibody.

Pavlinkova *et al* teach that the major advantages of scFv molecules are their excellent penetration into tumor tissue, rapid clearance rate and much lower exposure to normal organs than occurs with intact antibody (especially abstract).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used an scFv such as taught by Pavlinkova *et al* instead of the intact antibody or fragment used by the combined references.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to create an improved targeted molecule with the advantages taught by Pavlinkova *et al* with regard of use of scFv for targeting tumors.

11. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

12. Claims 1-4, 8, 10, 11 and 40 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 78 of copending Application No. 12/034,737 in view of Pavlinkova *et al* (Cancer immunology and immunotherapy, 2000, 49(4-5): 267-275), US 2002/0071842 A1 (of record) and Donda *et al* (Cancer Immunity 8/03, 3: 11).

Claim 78 of copending Application No. 12/034,737 is drawn to a CD1d complex comprising a soluble CD1d polypeptide/β2m and a ceramide-like glycolipid antigen bound to the CD1d/β2m and a carrier.

The said claim does not recite an antibody or scFv fragment thereof portion specific for a cell surface marker such as Her2/neu fused to the CD1d complex.

Pavlinkova *et al* teach that the major advantages of scFv molecules are their excellent penetration into tumor tissue, rapid clearance rate and much lower exposure to normal organs than occurs with intact antibody (especially abstract).

US 2002/0071842 A1 discloses a CD1d-IgG fusion protein comprising a tumor antigen, or alternately comprising α-GalCer as the antigen, that binds to CD1d, and administration of a composition comprising such in order to enhance or induce protective immunity to a condition associated with the presence of the tumor antigen (*i.e.,* a cancer). US 2002/0071842 A1 discloses that CD1 molecules are evolutionarily conserved β2m-associated proteins, with a similar domain organization to class I MHC antigen presenting molecules, although CD1 molecules have a deeper and more hydrophobic antigen binding groove that do class I MHC molecules. US 2002/0071842 A1 discloses that correspondingly, while class I MHC molecules present peptide antigens, CD1 molecules can present lipids, phospholipids and glycolipids, and both human and murine CD1d molecules have been shown to present α-GalCer, a synthetic acylphytosphingolipid originally isolated from a marine sponge, and that this latter antigen is recognized by CD1d-restricted NKT cells (especially Abstract, [0011], [0012], [0030], [0031], [032]-[0035], [0039], [0055], [0080]-[0083], [0095], [0101], [0124], [0127]-[0129], [0138], [0153], [0156], [0158], and claims).

Donda *et al* teach *in vivo* targeting of an anti-tumor antibody coupled to an antigenic MHC class I complex to induce specific growth inhibition and regression of established syngeneic tumor grafts. Donda *et al* teach that their strategy combined the advantage of the well-documented tumor targeting properties of anti-tumor antigen (*i.e.,* anti-TAA) mAbs with the known efficient and specific cytotoxic activity of CD8 T lymphocytes directed against highly antigenic MHC/peptide complexes, *i.e.,* using a Fab' fragment from a high affinity anti-TAA mAb coupled to a MHC class I containing a selected antigenic peptide in order to target the active MHC/peptide complex on tumor cells and induce their lysis by specific CTLs. Donda *et al* further teach using an anti-ErbB-2 antibody coupled to an MHC/peptide complex (*e.g.,* ErbB-2 is also known as Her2/neu) (see entire reference).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have added an scFv anti-Her2/neu targeting antibody fragment such as the scFv fragment taught by Pavlinkova *et al* with specificity for Her2/neu such as taught by Donda *et al* to the CD1d complex of claim 78 of copending Application No. 12/034,737 and to have used α-GalCer taught by Donda *et al* and disclosed by US 2002/0071842 A1 as the ceramide-like glycolipid antigen.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to produce an improved reagent for control of tumors, *i.e.,* a CD1d complex that could be targeted to tumor cells bearing the Her2/neu tumor associated antigen.

This is a provisional obviousness-type double patenting rejection.

13. The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned 12/034,737, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.
12. No claim is allowed.

14. The references crossed-out in Applicant's Form 1449 filed 11/15/06 have not been considered by the Examiner for the following reasons:

Reference "NPL26" is not a complete citation as the date is missing, and said reference has been stated by Applicant to be an English language equivalent for the other crossed-out reference "FP6".

15. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ram Shukla, can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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August 20, 2009

/G.R. Ewoldt/
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